Citation:

Hofman A, Hazebroek A, Valkenburg HA. A randomized trial of sodium intake and blood pressure in newborn infants. *JAMA.* 1983; 250: 370–373.

PubMed ID: 6343656

Study Design:

Double blind randomized trial

Class:

A - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To study the effect of sodium intake on the level and evolution of blood pressure (BP) in healthy newborn infants.

Inclusion Criteria:

Infants born at home or in an outpatient clinic to residents of Zoetermeer, Netherlands between January 15 and December 15, 1980.

Exclusion Criteria:

Infants born at a hospital (<50% of the deliveries in Holland).

Description of Study Protocol:

Recruitment

Prospective parents were contacted in the seventh month of pregnancy and babies of parents who gave informed consent were randomized to the control or intervention at birth.

Design

Double blind randomized trial.

Dietary Intake/Dietary Assessment Methodology

- A nurse recorded the amount of formula and solid food that was consumed
- Total intake of sodium (Na) was calculated from the food consumed along with an allowance for breastfeeding based upon the Na in the mother's breast milk
- Mothers were asked to record any deviation from the protocol.

Blinding Used

- A random number generator was used to assign parents to a sodium (Na) group
- The level of Na was known only to a person who prepared food packets and who had no direct contact with the parents
- Neither the parents nor the investigators were aware of the sodium assignment.

Intervention

- Participants received formula milk and solid foods delivered to their homes free of charge for six months
- Mothers could breast-feed their babies but were asked not to feed them any other foods besides the ones they received for the study
- Parents were advised to start solid foods during the 13th week after birth
- The normal Na milk contained an amount of Na that was regularly found in commercially available formulas during the study period
- The low Na formula had a concentration of Na that was similar to human breast milk. It was three times lower than the normal milk formula (6.3 vs. 19.2 mmol Na per L).
- The Na concentration of solid foods ranged from 2.2 to 13.0mmol per L in the low Na group and from 22.6 to 76.5mmol per L in the normal Na group
- The sodium/potassium ratio was 0.67 (low Na formula) and 0.64 (normal formula)
- Concentration of other minerals, protein and lipids in both milks were similar although chloride was lower (6.0mmol per L) in the low Na group compared with the normal Na group (22.6mmol per L).

Statistical Analysis

- The analyses were based on intent to treat as all subjects in whom BP readings were obtained, including infants who deviated from the protocol
- Difference in mean systolic blood pressure (SBP) measured at each session was adjusted for individual length and weight at birth, BP observer and SBP in the first week
- The adjusted and observed differences were used to give an estimate of the regression coefficient between the Na groups
- Data are presented with 90% CI and a P-value corresponding to a one-tailed test of significance.

Data Collection Summary:

Timing of Measurements

Blood pressure of each infant was measured at weeks one, five, nine, 13, 17, 21 and 25 by experienced study nurses.

Dependent Variable

Change in SBP:

- The measurements were performed by an experienced study nurse according to a standardized protocol with and Doppler ultrasound device connected to a random-zero sphygmomanometer that measured only SBP
- A 4cm cuff was used for all measurements
- The mean of three readings at each occasion was used for analysis.

Independent Variables

Sodium intake.

Control Variables

Length and weight at birth, BP observer and SBP in the first week.

Description of Actual Data Sample:

- *Initial N:*
  - 476 (73% of eligible subjects) gave informed consent at seventh month of pregnancy
  - Infants were randomly assigned to receive the normal Na diet (245) or the low-Na diet (231) starting immediately after birth
- *Attrition (final N):*
  - The analysis is of a total of 466 [241 (normal Na) and 225 (low Na)] subjects in whom BP readings were obtained
  - At 25 weeks BP in four infants in the low-Na group and six in the normal Na group could not be measures severe disease, death or migration
- *Age:* Newborn to six months old
- *Other relevant demographics:*
  - Percentage of females was 51 at baseline
  - Mean SBP in mothers and fathers were within healthy range
  - At birth breastfeeding was 72% in the normal Na and 68% in the low-Na group
  - At month six, breastfeeding was 15% in the normal Na and 13% in the low-Na group
- *Anthropometric characteristics at entry into study:* Mean (SD) for Normal; Low Na
  - SBP (mmHg) 87.7 (19.7); 87.7 (19.5)
  - Length (cm) 50.9 (2.2); 51.0 (2.1)
  - Weight (g) 3,421 (481); 3,466 (429)
- *Location:* Zoetermeer, Netherlands.

Summary of Results:

Dep var Systolic Blood Pressure

Weekly SBP (mmHg) and Observed and Adjusted Differences in Mean SBP Between Study Groups

Mean SBP in Normal Na and Low Na Groups					BP Normal Na Group Minus Low Na Group			
Normal Na			Low Na		Observed Difference		Adjusted Difference	
Week	Mean	SD	Mean	SD	Mean	95% CI	Mean	95% CI
1	87.7	19.7	87.0	19.5	0.7	-2.3 to 3.7	*	
5	101.9	18.6	102.5	19.0	-0.6	-3.4 to 2.2	-0.4	-2.1 to 2.9
9	108.8	14.8	108.3	14.9	0.5	-1.8 to 2.8	0.4	-1.7 to 2.5
13	111.9	13.4	111.3	13.7	0.7	-1.4 to 2.8	0.6	-01.4 to 2.6

17	113.4	13.6	112.4	11.9	1.0	-1.0 to 3.0	1.2	-0.6 to 3.0
21	114.9	11.0	113.5	12.2	1.4	-0.4 to 3.2	1.7	0.0 to 3.4
25	116.1	11.2	114.1	11.9	2.0	0.2 to 3.8	2.1	0.5 to 3.7

* Included in adjusted model.

- SBP increased with age in both groups
- At 25 weeks, unadjusted SBP measurement was 2.0 higher in the normal Na group compared with the low Na group (P=0.03)
- The adjusted difference of 2.1mmHg also increased significantly in the normal sodium group at 25 weeks (P=0.025).

Sodium Intake and Excretion Measures (Mean±SD)

Measure	Low Na	Normal Na
Food contribution to Na		
Formula	72%	72%
Breast milk	23%	10%
Solid food	5%	18%
Average Na (mol) consumed during study period	0.89±0.26	2.50±0.95
Average urinary NA (mmol per L) excreted weeks five, 13, 21	11.1±10.0	22.7±14.5

Other Key Findings

- At birth, deviation from protocol was 0.8% in the normal Na and 2.6% in the low-Na group
- At month six, deviation from protocol was 8.2% in the normal Na and 10.8% in the low-Na group
- As a surrogate for extracellular fluid expansion, there was no difference in body weight to indicate that babies on the normal Na diet had more fluid retention. Average body weight was not different among groups until 21 and 25 weeks when it was the low Na group that was slightly higher.

Author Conclusion:

- The authors conclude that dietary Na intake is associated with SBP in infants from birth to six months
- They suggest that moderation of Na intake starting very early in life might contribute to prevention of high BP as the child gets older.

Reviewer Comments:

Strengths

- *Dietary intake of Na in infants was effectively moderated in this study as demonstrated by the urinary excretion of Na that correlated with the formula, breast milk and food estimated Na*

- *High follow-up rates and a large sample size, which compensated for the relatively few number of BP measurements (only one BP per month).*

Limitations

While the study shows an association between Na and BP in infants the study period may not be long enough to predict a long-lasting increase in BP.

Comments

- *It would be interesting to see how the BP varies among infants after the interventions were complete*
- *This study might also raise the question about why commercial infant formula would be made with sodium concentration three times higher than human milk.*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions		
1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes

2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	???
3.	**Were study groups comparable?**	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	N/A
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	Yes
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	Yes
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes

5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	Yes
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	N/A
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	???
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	???
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	Yes

8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	No
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	Yes
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**	Yes
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes